

SUPPORT FOR THE AMENDMENTS

Claims 1-7 and 9 were previously canceled.

Claims 8 and 11 have been amended.

Support for the amendment to Claims 8 and 11 is found at page 3, lines 4-16, pages 6-7, page 8 lines 15-25, page 8, lines 32-39, page 8, lines 28-30 and page 9, lines 1-9, as well as Examples 3 and 4.

No new matter has been added.

REMARKS

Claims 8, 10, and 11 are pending in the present application.

The rejection of Claims 8, 10, and 11 under 35 U.S.C. §112, first paragraph (enablement), is obviated by amendment.

In the Office Action, the Examiner recognizes that the specification enables method for increasing the cytostatic or cytotoxic effects on colon and liver tumor cells and decreasing the cytotoxic effect on normal leukocytes or cisplatin, oxaliplatin, 5-FU, and taxol. Accordingly, Applicants make no statement with respect to the propriety of the Examiner's allegations with respect to lack of enablement for the broader scope of the previously pending claims and in no way acquiesce to the same. Solely to expedite examination of this application, Applicants have limited the platinum derivatives in Claims 8 and 11 to cisplatin and oxaliplatin. Thus, this ground of rejection is believed to be moot.

It is further noted that in the present application (cf Example 3), the effect of the combination of mangafodipir with a platinum derivative is shown not only in colon tumor cells (cell line CT26), and liver tumor cells (cell line Hepa 16), et but also in lung cancer cells (cell line A549). Further, it is also shown in the application (Exemple 4) that mangafodipir acts by increasing the alterations induced by platinum derivatives in the structure of DNA. Therefore, one reasonably expect that these effects of mangafodipir will be the same with all cisplatin- or oxaliplatine-sensitive tumor cells.

Withdrawal of this ground of rejection is requested.

The rejection of Claims 8, 10, and 11 under 35 U.S.C. §112, first paragraph (written description), is obviated by amendment.

In the Office Action, the Examiner recognizes that the specification provides sufficient written description of the platinum compounds cisplatin and oxaliplatin,. Accordingly, Applicants make no statement with respect to the propriety of the Examiner's allegations with respect to lack of written description for the broader scope of the previously pending claims and in no way acquiesce to the same. Solely to expedite examination of this application, Applicants have limited the platinum derivatives in Claims 8 and 11 to cisplatin and oxaliplatin. Thus, this ground of rejection is believed to be moot.

Withdrawal of this ground of rejection is requested.

The rejection of Claims 8, 10, and 11 under 35 U.S.C. §103(a) over Federle et al in view of Towart et al and Vaage et al as evidenced by Teslascan is obviated by amendment.

Federle et al disclose the use of mangafodipir as a diagnostic agent, namely a contrast agent in magnetic resonance imaging. Federle et al do not disclose any therapeutic use thereof. In particular, Federle et al do not disclose any antitumoral or leukocyte-protecting effect of mangafodipir. And, as recognized by the Examiner, Federle et al do not disclose any combination of mangafodipir with an anticancer medicinal product, in particular with cisplatin or oxaliplatin. Notwithstanding the Examiner's allegations to the contrary, none of Towart et al, Vaage et al or Teslascan compensate for this deficiency in the disclosure of Federle et al.

Towart et al disclose that chelating agents, including mangafodipir are effective in reducing the cardiotoxicity of anthracyclines and paclitaxel. Towart et al do not suggest that mangafodipir may be useful in combination with other antitumor agents than anthracyclines

and paclitaxel. In particular, Towart et al do not suggest at all that they can be used in combination with cisplatin or oxaliplatin, which have a mechanism of action which is quite different from the ones of anthracyclines and paclitaxel. Therefore cisplatin and oxaliplatin also quite different side-effects.

It was well known at the time the invention was made that different antitumoral drugs had different side effects, and that quite different drugs were used against these side effects. For instance, while the chelating agent Dexrazoxane was the more commonly used medication against the cardiotoxic side effects of anthracyclines, a quite different drug, Amifostine, was used against the side effects of platinum derivatives (see Schuchter et al. *Journal of Clinical Oncology*, Vol 20(12), 2002, 2895-2903, **submitted herewith**, especially pages 2896 to 2899 for the use of Dexrazoxane, and pages 2899 to 2900 for the use of Amifostine in combination with chemotherapy).

Further, Towart et al do not suggest that mangafodipir may have other effects than reducing cardiotoxicity of anthracyclines and paclitaxel. The experiments disclosed in Towart et al were performed with mice who had no tumors. Although they showed a protective effect of mangafodipir against antracycline-induced cardiotoxicity, they did not disclose or suggest any antitumoral effect. Also, Towart et al do not suggest any leukocyte protecting effect of mangafodipir. Actually, they rather indicate (page 8, 5th §, last sentence) that “myelotoxicity associated with paclitaxel administration [...] can be substantially reduced by co-administration of granulocyte-colony stimulating factor (G-CSF)”. Therefore, Towart et al do not suggest at all that mangafodipir may reduce myelotoxicity (i.e have a leukocyte-protecting effect). Instead Towart et al teach that an additional component (G-CSF) is to be used. This disclosure would have suggested to one of skill in the art that mangafodipir was inefficient to reduce myelotoxicity.

Vaage et al disclose that ineffectively low doses (i.e doses which have no effects when administered in the usual saline formulations) of cisplatin and doxorubicin are able, when encapsulated in long-circulating pegylated liposomes, to inhibit the growth of a human colonic carcinoma in nude mice, while having minor or no toxic side effects. Vaage et al disclose an approach (liposome encapsulation) for enhancing the efficiency and reducing the side effects of anti-cancer drugs, which is quite different from the one (illustrated for instance by Schuchter et al) which consists in combining a specific anti-cancer drug with a specific compound in order to counteract one or more of specific the side effects of said anti-cancer drug and/or to increase its antitumoral efficiency.

The effects of liposome encapsulation are generally not specific of the encapsulated drug. They rely more generally on a slow release of the drug, which allow to obtain a sustained action and to avoid high peak plasma concentrations responsible of many side effects, and on a change in tissue distribution allowing a better targeting of the anti-cancer drug to the target tumor cells and therefore the use of low doses reducing the occurrence of unwanted side effects. These effects of liposome encapsulation are clearly explained in the “Discussion” of Vaage et al (Applicants **submit herewith** a full-text copy of Vaage et al for the Examiner’s reference).

Therefore, it is clear that one of skill in the art would have had no motivation to replace the liposome encapsulation of cisplatin by its combination with mangafodipir. Accordingly, Applicants submit that the presently claimed invention is not obvious in view of the combined disclosures of Federle et al, Towart et al, Vaage et al, and Teslascan.

Withdrawal of this ground of rejection is requested.

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, L.L.P.
Norman F. Oblon



Vincent K. Shier
Registration No. 50,552

Customer Number

22850

Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 08/03)